REMARKS

I. Amendments to the Specification

Per the Examiner's request, paragraphs [0033], [0068], [0069], and the paragraph at page 53, lines 12-15 have been amended to inactivate hyperlinks. Paragraph [0005] has been amended to correct editorial errors. By this Amendment, no new matter has been added to the specification.

II. Status of the Claims

Claims 1-59 are pending. In response to a restriction requirement, Applicants elected claims 37-46 and 48 for prosecution on the merits. Therefore, claims 1-36, 47 and 49-59 have been withdrawn. Claims 37 and 38 and 42 have been amended for clarity. Claims 38 and 42 have been amended to delete the first step of obtaining a sample from a subject. Claims 39-41 and 42-45 have been canceled. By this Amendment, no new matter has been added to the claims.

III. Claim Objections

The Examiner has objected to claim 38, because of the redundant nature of the term "immune responses," and objected to claim 42, based on a grammatical error. In response, the term "immune responses" has been deleted from claim 38 and claim 42 has been amended to delete the phrase "wherein the." Accordingly, these two objections are believed to have been overcome. Withdrawal of the objections is requested.

IV. Rejections under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 37-46 and 48 as not being enabled for "determining T-cell epitopes," "predicting the reaction of an individual to a vaccine" or "a method of matching a vaccine." The rejection is respectfully traversed.

The standard for enablement is whether the application contains sufficient information to enable one of ordinary skill in the pertinent art to make and use the claimed invention without undue

experimentation. Among the factors to be considered in determining whether the claims are enabled is the amount of guidance provided in the application. *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). The instant specification provides detailed guidance on how to practice the claimed invention.

Claim 37 is directed to a method of determining T-cell epitopes within amyloid β peptide, comprising (a) determining the binding value of each amino acid of a subsequence of amyloid beta peptide or homologue thereof upon binding to a HLA class I and/or class II molecule of interest; (b) determining the resulting score of all amino acids of the subsequence based on the binding value of each amino acid obtained in step a; and (c) comparing said resulting score to a preselected value, to predict presence of T-cell epitopes within amyloid beta peptide or homologue thereof.

The specification teaches how to carry out step (a), determining the binding value of each amino acid of a subsequence, in paragraphs [0030], [0033], [0034] and [0064] of the published application. Thus, the specification sets forth:

> The binding value of the amino acid can be represented according to one embodiment of the invention, as the contribution of this amino acid to the half life time for disassociation of the subsequence to the HLA class I and/or class II molecule. It should be noted that the binding value of a specific amino acid may be varied according to its position in the sequence.

See specification at paragraph [0030].

The specification further teaches how to determine the binding value of each amino acid obtained in step (a):

> Publicly accessible algorithms from the BioInformatics & Molecular Analysis Section (BIMAS) of the National Institutes of Health rank potential peptides based on predicted half-time of dissociation to HLA class I molecules. They

> are based on coefficient tables deduced from the published literature by Dr. Kenneth Parker (Parker 1994), Applied Biosystems (see website //bimas.dcrt.nih.gov/molbio/hla_bind/).

Specification at paragraph [0033].

The specification further teaches how to carry out step (b). Paragraph [0033] of the specification, for example, sets forth:

> The step of determining the resulting score of all amino acids of the subsequence based on each of the binding values of each amino acids obtained in step a is conducted by addition of each of the amino acid values and by simply adding the values or multiplication.

The way in which binding values are combined is specific for each algorithm employed. For example, the algorithm created by Parker uses multiplication.

The application also teaches how to carry out step (c):

> The resulting score is compared to preselected value or preselected score, to predict presence of undesirable T-cell epitopes within amyloid beta peptide or homologue thereof.
>
> The term "preselected score" refers hereinafter to a value, which represents a threshold value. Any value which is lower than that value represents subsequences with low probability of inducing T-cell responses. Any number which is higher than this value predicts the presence of a T-cell epitope which may induce T-cell responses.

Specification at paragraphs [0033] and [0034] (underlining added).

In summary, the application provides detailed guidance in how to carry out steps (a)-(c) of claim 37. No further information is required by a person of ordinary skill in the art to practice claim 37. Thus, the specification enables the full scope of claim 37.

The specification also enables claims the full scope of 38 and 42. Step (a) in both of claims 38 and 42 calls for determining the HLA haplotype of an individual. Paragraphs [0045]-[0048] provide detailed guidance for determining HLA haplotype:

> For example, in addition to the traditional, serological methods of typifying HLA, a series of DNA analysis methods have been described. Based on the polymerase chain reaction, a certain allele can be typified by amplification with sequence-specific primers (SSP-PCR), by hybridization with sequence-specific oligonucleotides (SSOP-PCR) or by the use of restriction length polymorphism.
>
> Some RFLP and similar typing methods utilize labelled obligonucleotides to identify specific HLA and DNA sequences. In particular, the use of oligonucleotide probes have been found advantageous in HLA-DR typing in identifying variant genes encoding products which are not detectable serologically.
>
> The polymerase chain reaction (PCR) process, as described in Mullis U.S. Pat. No. 4,683,202, issued Jul. 28, 1987, allows the amplification of genomic DNA and has given rise to more convenient BLA typing procedures. HLA-DQ alpha and HLA-DP alpha and beta genes have been amplified, and then sequenced or hybridized with oligonucleotide probes.

Steps (c), (d) and (e) of claims 38 and 42 correspond to steps (a), (b) and (c) of claim 37. As set forth above, the specification provides detailed guidance for carrying out these steps. Thus, the specification provides detailed guidance on how to perform each step of claims 38 and 42.

In summary, the specification sets forth all of the information required to practice the invention of claims 37, 38 and 42. The detailed guidance in the specification thus allows one of ordinary skill in the art to make and use the invention of claims 37, 38 and 42 without undue experimentation.

Examination of other factors set out in Wands further demonstrates the specification is enabling for the full breadth of the claims. Examples I, II and VI (paragraphs [0062], [0063] and [0070] of the specification) provide working examples as to how to practice claim 37, and the final three steps of claims 38 and 42. Additionally, the level of skill in the art of immunology and molecular biology is high.

For at least the reasons set forth above, the specification is enabling for the full breadth of the claims. Thus, the rejection of the claims for lack of enablement should be withdrawn.

In further response in setting forth the enablement rejection, the Examiner provides certain assertions that are not believed to be well founded. The Examiner states there is no nexus between scoring a peptide greater or less than a preselected value and matching a vaccine, or predicting a reaction, or determining if a T-cell epitope is present on an amyloid β peptide (the preambles of the rejected claims). The nexus exists, however, because the "scores" recited to in the claims are indicative of the presence of a T-cell epitope (*see* specification at paragraph [0034]). Thus, a "preselected score" is simply a value below which a T-cell epitope has a low probability of being present, and above which a T-cell epitope has a high probability of being present (*see* specification at paragraph [0034]). Moreover, the Examiner acknowledges that the application is enabling for selecting a peptide using the HLA peptide binding predictions program to identify sequences that probably bind to different haplotypes (Office Action, page 3). These correspond to steps (a), (b) and (d) of claim 37, steps (b), (c) and (d) of claim 38, and steps (a), (b) and (c) of claim 42.

Furthermore, the Examiner's assertion on page 3 of the Official Action that "determining T-cell epitopes," "predicting the reaction of an individual to a vaccine," and "a method of matching

a vaccine" are not enabled is not well founded. If a binding score is above a threshold, a T-cell epitope is present (claim 37), which predicts T-cell responses (*i.e.*, a reaction to a vaccine, claim 38). Similarly, if a score is above the threshold, the peptide would not be matched as a vaccine (claim 42), because the T-cell epitopes present on the peptide would be able to induce an immune response.

The Examiner also asserts that the "art says predicting autoimmunity cannot be done." The Examiner's assertion, however, is drawn too broadly. The instant claims are not directed to "predicting autoimmunity." The claims are drawn to predicting the probability of eliciting a T-cell response. As set forth above, the scope of the claimed invention is commensurate in scope with the disclosure of the specification. Thus, the Examiner's reference to more general teachings is not controlling.

The Examiner asserts undue experimentation is necessary in determining the reaction of a patient to a vaccine. Determining a reaction of a patient, however, is not a requirement to practice the claimed invention. The specification need not establish that a claimed method of treatment be safe and effective to enable the claims. Although "safe and effective" may be the proper standard for FDA approval of a drug, it is not the proper standard for enablement.

For all the reasons set forth above, the specification enables the full scope of the claims. Reconsideration of claims 37, 38, 42, 46 and 48 and withdrawal of the rejection thereof for lack of enablement is requested.

V. Rejections under 35 U.S.C. §112 first paragraph (written description)

The Examiner rejected claims 37-46 and 48 as failing to comply with the written description requirement. The Examiner states no "preselected value" is disclosed in the

specification, nor is it disclosed how that "preselected value" determines T-cell epitopes or predicts the reaction of an individual or matches a vaccine to a patient.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. The specification of the application contains sufficient details to establish that the inventors had in possession the claimed invention, as discussed below.

Paragraph [0034] of the application sets forth:

> The term "preselected score" refers hereinafter to a value, which represents a threshold value. Any value which is lower than that value represents subsequences with low probability of inducing T-cell responses. Any number which is higher than this value predicts the presence of a T-cell epitope which may induce T-cell responses (for example without being limited Example 6, Table 7 SEQ ID No. 133 and 134 have scores higher than the threshold of 49.00).

At least this portion of the disclosure establishes the inventors were in possession of the "preselected value," called for in the claims and were able to apply that value to scoring amyloid β peptides with regard to the presence of T-cell epitopes.

Based on the program used to identify T-cell epitopes, those of ordinary skill in the art would know what value to select for a threshold "preselected value." For example, one of ordinary skill in the art could readily apply one of the disclosed algorithms to a sequence which corresponds to a peptide or protein that is known to have a T-cell epitope, or that is known to elicit T-cell responses. The value obtained for the test sequence would correspond to the threshold "preselected value," wherein values above the "preselected value" are said to have T-cell epitopes. In addition, the value could be adjusted to control for weaker binding. Depending on the method itself, one preselected value may be preferred over others.

Based on the above arguments, Applicants ask for withdrawal of the written description rejections of claims 37-46 and 48.

VI. Rejections 35 U.S.C. §112 second paragraph (indefiniteness)

Claims 37-46 and 48 stand rejected for allegedly being indefinite. The Examiner contends there is insufficient antecedent basis for the term "a preselected value." In response, without conceding the validity of the rejection, Applicants have amended claim 37 to call for a preselected value that is indicative of the presence of a T-cell epitope." Applicants respectfully request withdrawal of the rejection.

The Examiner also alleges that determining a "binding value" is indefinite. This rejection is traversed, as follows. Section 112, second paragraph requires that one of ordinary skill in the art understand the metes and bounds of the claimed invention. The instant specification discloses the meaning of the term "binding value." Paragraph [0031] states that "the binding value of the amino acid can be represented according to one embodiment of the invention, as the contribution of this amino acid to the half life time for disassociation of the subsequence to the HLA class I and/or class II molecule." One of ordinary skill in the art would understand an amino acid's "binding value" to mean a score indicative of the amino acid's contribution to the overall strength of binding to the HLA molecule (*i.e.*, Kd value).

VII. Rejections under 35 U.S.C. §102(b) (anticipation)

The Examiner asserts that claim 37 is anticipated by Parker *et al J. Immunol.* 152:163-175 (1994) ("Parker"). The Examiner contends that Parker determines epitopes within many peptides which are homologues of amyloid β by determining a binding value of each amino acid, determining the resulting score, and comparing the resulting score to a preselected value to predict the presence of binding epitopes or "T-cell epitopes."

Applicants respectfully traverse the rejection as follows. Claim 37 calls for the prediction of the presence of T-cell epitopes within amyloid beta peptide or homologue thereof.

The Examiner's assertion that Table VII in Parker discloses homologues of amyloid β is not well founded. The peptides are described to be homologues of β_2M, not amyloid β. In addition, no peptide listed in table VII of Parker exhibited at least 70% identity to Aβ peptide (SEQ ID NO: 2) (*i.e.*, homology, as defined in the specification at paragraph [0022]). Because Parker does not disclose each limitation of claim 37, Parker does not anticipate claim 37. Reconsideration of claim 37 and withdrawal of the instant rejection is requested, accordingly.

VIII. Conclusion

Based on the above amendments and arguments, this application is believed to be in condition for allowance, which is earnestly solicited. If there are remaining issues that the Examiner believes could be addressed by conducting an interview or entering an Examiner's Amendment, the Examiner is cordially invited to contact the undersigned attorney to discuss such issues.

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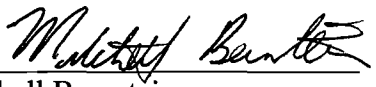
Respectfully submitted,

By 

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